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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/830,019	09/21/2001	Chikara Aizawa	SHIM1120	9316
28213	7590	04/17/2006	EXAMINER	
DLA PIPER RUDNICK GRAY CARY US, LLP			LE, EMILY M	
4365 EXECUTIVE DRIVE				
SUITE 1100			ART UNIT	PAPER NUMBER
SAN DIEGO, CA 92121-2133			1648	

DATE MAILED: 04/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/830,019	AIZAWA ET AL.
	Examiner	Art Unit
	Emily Le	1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 06/24/2005+1/23/2006
 2a) This action is FINAL. 2b) This action is non-final.
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-3 and 7 is/are pending in the application.
 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
 5) Claim(s) _____ is/are allowed.
 6) Claim(s) 1-3 and 7 is/are rejected.
 7) Claim(s) 2 is/are objected to.
 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ . |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>1/23/06 or 6/24/05</u> . | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 1/23/2006 has been entered.

Status of Claims

2. Claims 4-6 and 8-15 are cancelled. Claim 1 has been amended. Claims 1-3 and 7 are pending and under examination.

Claim Objections

3. Claim 2 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 2 requires the toxin to be a mutant having an amino acid sequence corresponding to the natural toxin, wherein one or more amino acid residues are substituted, inserted, deleted and/or added. However, it is noted that claim 2 depends on claim 1, wherein it is gathered that claim 1 requires the purified and attenuated toxin to retain serine and glutamic acid residues present in the natural toxin. In the instant, it

is found that claim 2 fails to further limit claim 1 because claim 2 does not set forth the retention of serine and glutamic residues present in the natural toxin.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 1-3 and 7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rendered indefinite by the following recitation: "except that and lysine residues of the natural toxin in its amino acid sequence, except that a formalin molecule is bound to the lysine residues of the attenuated toxin". In the instant, it is unclear what is intended by the cited recitation.

Claims 2-3 depend on claim 1. Claim 1 refers to two different toxins, a purified and attenuated toxin and a natural toxin. In the instant, claims 2-3 contain recitations directed at a toxin, however, it is unclear which toxin the claims are directed. For instance, by the recitation "said toxin", as set forth in the first sentence of each respective claim, is Applicant referencing the i) purified and attenuated toxin or ii) natural toxin? Clarification is required.

Additionally, claim 3 is further rendered indefinite for the following reason(s): As stated above, claim 3 depends on claim 1. Claim 1 specifically requires that the purified and attenuated toxin to be less toxic than the natural toxin. However, it is noted that claim 3 further limits the toxin to a natural toxin. In the instant, it is unclear how a

natural toxin can have a toxicity that is any different than that observed in its natural form?

Claim 7 recites a dependency to claim 6, however, claim 6 has been cancelled. The cancellation of claim 6 renders claim 7 incomplete. Thus, because claim 7 is incomplete, the claim is rejected under 35 U.S.C. 112, second paragraph for it is unclear what is intended to be encompassed by claim 7. For the purpose of examination, the Office presumes that the intended dependency for claim 7 is claim 1 instead of claim 6.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. In response to the prior art rejection of claims 1, 3, 6, 7 and 13 under 35 U.S.C. 102(b) as being anticipated by Esposito et al., Applicant cancelled claim 6 and amended independent claim 1, requiring the attenuated toxin be purified.

In view of Applicant's submission, the rejection of claims 1, 3, 6, 7 and 13 under U.S.C. 102(b) is withdrawn, particularly since Esposito et al. does not teach the purification of the toxin.

8. Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Germanier et al.¹

¹ Germanier et al. Preparation of a purified antigenic cholera toxoid. Infection and Immunity, 1976, Vol. 13, No. 6, 1692-1698.

The claim is directed at a purified and attenuated cholera toxin, wherein the toxin has a residual toxic activity of less than 1/2000 that of the natural toxin and having an activity of enhancing the production of an antibody specific to an antigen other than the attenuated toxin.

It is noted that the claim contains the following recitation: "except that and lysine residues of the natural toxin in its amino acid sequence, except that a formalin molecule is bound to the lysine residues of the attenuated toxin"; however, because it is unclear what is intended by the cited recitation, the recitation has been withdrawn from examination.

Germanier et al. teaches a purified and attenuated cholera toxin, wherein the toxin has a residual toxic activity of less than 1/2000 that of the natural toxin. [Abstract] In the instant, Germanier et al. teaches the claimed invention. Thus, Germanier et al. anticipates the claimed invention.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Germanier et al., as applied to claim 1.

The claim limits the residual toxic activity of **less than 1/10000**.

The significance of Germanier et al. as it pertains to claim 7 is discussed above.

The difference between the claimed invention and Germanier et al. is: The residual toxic activity of the purified and attenuated cholera toxin of Germanier et al. is noted to be 1/10000 that of its natural toxin. [Abstract] It is not readily apparent if the purified and attenuated cholera toxin of Germanier et al. is has a residual toxic activity of **less than** 1/10000 than it's natural toxin.

However, MPEP § 2144.05 [R3] [II] states: Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be *prima facie* obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%.); see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 (“The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.”); In re Hoeschele, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see Merck & Co. Inc. v. Biocraft Laboratories Inc.,

874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); In re Kulling, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

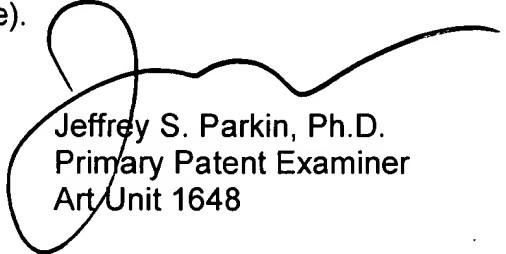
In the instant, the specification does not contain any evidence indicating that the claimed level of toxicity is critical. Additionally, the general conditions of the claimed invention are disclosed by Germanier et al. Germanier et al. teaches the detoxification of the cholera toxin. Germanier et al. also teaches the administration of the detoxified toxin with whole cell vaccines against *Vibrio cholerae* infection. Thus, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to remove all toxicity from the toxin to ensure its safe use with whole cell vaccines against *Vibrio cholerae* infection.

Conclusion

11. No claims are allowed.
12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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